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(54) **Coating medical devices with cationic antibiotics.**

(57) A medical device having long-lasting bactericidal properties and a method for making the same is provided. The material from which the medical device is made, the substrate, carries a negatively-charged group having a pKa of less than 6. A cationic antibiotic is ionically bonded to the negatively-charged group. The negatively-charged group may be a portion of a larger carrier molecule. The carrier molecule is bound to the substrate such that the negatively-charged group is exposed for ionic interaction with the cationic antibiotic. Heparin is an ideal carrier molecule because it has both anti-bacterial adhesion activity and anti-thrombogenic activity.

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COATING MEDICAL DEVICES WITH CATIONIC ANTIBIOTICS

This invention relates to implantable medical devices having germicidal and antithrombogenic properties, and in particular relates to securing cationic antibiotics to medical devices.

Medical procedures may fail due to complications arising from infection. Not only may an infection undermine the efficacy of the procedure, but it may be life-threatening itself.

For procedures involving implantable medical devices, avoiding infection is particularly problematic. Normally, free floating or platonc microbes in blood, tissue or organs are destroyed by antibodies, white blood cells, macrophages and antibiotics. With implants, microbes introduced pre- or intra-operatively may adhere to the foreign material of the implant and then transform into biofilm. Such biofilm consists of dormant microbes covered with a layer of glycocalyx secretion which protects the microbes from antibodies, macrophages and antibiotics. The microbes then may remain dormant as long as their proliferation into surrounding tissues can be checked by the body's immune system or systemic treatment with antibiotics. However, if the body's immune system is defective or if systemic administration of antibiotics is discontinued, the microbes may proliferate rapidly and invade surrounding tissue. For a more detailed description of biofilm, see "Bacterial Adherence and the Glycocalyx and Their Role in Musculoskeletal Infection", Cristina, A. G. and Costerton, J. W., *Orthop. Clin. N. Amer.*, 15:517, 1984, and "Bacterial Biofilm in Persistent Penile Prosthesis Associated Infection", Nickel, J. C., Heaton, J., Morales, A. and Costerton, J. W., *The Journal of Urology*, 135:586-8, 1986.

Efforts to reduce the risk of this type of infection have included providing the implant with germicidal properties such that the microbes will be destroyed when they contact the implant. For example, implants coated with anionic antibiotics have been developed for reducing the risk of infection. To be effective, the antibiotic must be secured in a manner that preserves its germicidal activity. It is also critical that the antibiotic be secured firmly to the medical device so that its germicidal properties are localized and sufficiently long lasting.

Recent efforts have been focused on securing anionic antibiotics to medical devices. Many infectious agents, however, are resistant to the commonly available families of anionic antibiotics. The selection of cationic antibiotics is much broader than the selection of anionic antibiotics. The present invention provides a method for securing cationic antibiotics to medical devices.

Medical procedures involving implantable

medical devices sometimes fail due to the thrombogenicity of the medical device. Many materials having the preferred physical characteristics for performing the functions of the medical device are thrombogenic. For example, as stated in U. S. Patent 4,116,898, "polymers, both natural and synthetic, and particularly certain synthetic plastics have come to the fore as preferred materials. . . Their major drawback, however, is their thrombogenicity." To overcome this problem, antithrombogenic agents have been secured to medical devices.

For procedures involving a risk of failure both from infection and the thrombogenicity of the medical device, it has been suggested to secure both antibiotics and antithrombogenic agents side-by-side on the medical device. Doing so, however, dilutes the amount of either the antibiotic or antithrombogenic agent that can be attached to the device. This in turn reduces the germicidal and antithrombogenic properties of the medical device.

It is an object of the present invention to provide a medical device having long-lasting activity against infectious agents sensitive to cationic antibiotics.

It is a further object of the invention to provide a medical device having both enhanced germicidal activity, anti-bacterial adhesion activity and antithrombogenic activity.

It is still another object of the invention to provide a method for more firmly bonding cationic antibiotics to medical devices.

It is still another object of the invention to provide a method for binding cationic antibiotics to a wide range of materials.

It is still another object of the invention to provide a medical device with the above-mentioned properties that is inexpensive to prepare and capable of being packaged and stored.

According to the invention, a medical device having long-lasting bactericidal properties is provided. The material from which the medical device is made, the substrate, carries a negatively-charged group having a pKa of less than 6. A cationic antibiotic is ionically bonded to the negatively-charged group. The negatively-charged group may be a portion of a larger carrier molecule. The carrier molecule is bound to the substrate such that the negatively-charged group is exposed for ionic interaction with the cationic antibiotic. Heparin is an ideal carrier molecule because it has both anti-bacterial adhesion activity and antithrombogenic activity.

Also according to the invention, a method for preparing a medical device having long-lasting bac-

tericidal properties is provided. The substrate is provided with a negatively-charged group having a pKa value of less than 6. The substrate is then soaked in a cationic antibiotic-containing solution and allowed to dry.

Medical devices according to the present invention may be fabricated from virtually any biocompatible substrate. It is only necessary that the substrate be capable of carrying negatively-charged groups having pKa values of less than 6. Dacron, latex, silicone, polyethylene and PVC have all been tested successfully.

Medical devices are provided with negatively-charged groups having a pKa of less than 6 and then are soaked in solutions of cationic antibiotics to ionically bind the cationic antibiotic to the medical device. It has been found that the negatively-charged groups having a pKa value of less than 6 will bind cationic antibiotics more firmly than negatively-charged groups having pKa values of greater than 6. This firmer bond does not impair the efficacy of the antibiotic's germicidal activity and holds the antibiotic on the medical device for an extended period of time. In particular, it has been found that sulphate groups, sulfonate groups and phosphate groups, having pKa values of less than 1, about 1 and 2.1 respectively, bind cationic antibiotic much more firmly than carboxyl groups (COOH) having a pKa value of greater than 6.

The negatively-charged groups may be manufactured into the surface of the medical device. Sulfonated polystyrene, for example, may be manufactured to carry suitably charged surface groups. Likewise, negatively charged groups may be attached directly to the surface of the medical device. Suitable techniques include the immobilization of negative groups carried on polymers or biopolymers by radiation or chemical cross-linking.

Negatively-charged groups may also be coated onto the surface of the medical device. In particular, a negatively-charged group may be a portion of a larger carrier molecule which is coated or otherwise attached onto the surface of the medical device. For example, phospholipids include both a phosphate group and at least one long hydrophobic side chain. A medical device manufactured from a hydrophobic substrate may be soaked in a solution containing the phospholipid. The hydrophobic side chain of the phospholipid will bind to the hydrophobic material in a manner to expose the phosphate group for binding with the cationic antibiotic. Any molecule generally described by the formulas ROSO_3^- , RSO_3^- and ROPO_3^- , where R is a long hydrophobic side chain is a suitable carrier molecule. For example, R may be composed substantially of carbon and hydrogen and be at least four carbon atoms long.

The most preferred carrier molecule is heparin,

which is capable of binding more than one cationic antibiotic since it has many sulphate groups. In addition, the heparin has anti-bacterial adhesion and antithrombogenic activity. By coating the medical device with heparin, many more sulphate groups cover the medical device's surface providing more cationic binding sites over a given area than has heretofore been achieved. The substrate may then be packed rich with cationic antibiotic.

Once implanted, the cationic antibiotic will slowly be released from the heparin carrier molecule by dissociation. As cationic antibiotic is released, the heparin molecule is exposed. The exposed heparin is known to have antithrombogenic activity. The heparin also may prevent bacteria from adhering to the substrate thereby preventing the formation of a protective biofilm. Without a protective biofilm, the microbes are vulnerable to antibodies, white blood cells, macrophages and antibiotics. A heparin-coated substrate may reduce bacterial adherence by as much as ten fold. Heparin and its antibacterial properties are more particularly described in "Reduction of Bacterial Adherence to Latex Catheter Surface with Heparin", Ruggieri, M. R., The Journal of Urology, AUA Eighty-First Annual Meeting Abstract K/2, 533, 1986. Thus, a heparin carrier molecule serves three separate functions. It provides a dense packing of sulphate cationic binding sites, provides antibacterial adherence activities, and provides antithrombogenic activity.

Preferably the heparin is attached to the substrate by an anchor molecule interposed between the medical device and heparin. As described in U. S. Patent 4,442,133, surfactants such as tridodecyl methyl ammonium chloride (TDMAC) and benzalconium (BZK) may be used to firmly bind a negatively-charged molecule to a hydrophobic substrate. While an anchor molecule, and in particular TDMAC, is preferred, it should be recognized that other methods of attachment are possible. For example, the medical device may be manufactured with or otherwise provided with positive surface charges. Heparin molecules then may be secured to the medical device via ionic interaction between the negatively-charged heparin and the positive surface charges on the medical device. The heparin molecules also could be immobilized onto the medical device by radiation or various cross-linking reagents, such as cyanogen bromide.

Suitable cationic antibiotics include those classified as polypeptides, aminoglycosides, and bases. Among the polypeptides are bacitracin, polymyxins, tyrothricin, viomycin, vancomycin, and their derivatives. Aminoglycosides include neomycin, erythromycin, streptomycin, tobramycin, gentamicin, kanamycin, paromomycin, and their derivatives. Bases include cycloserine, tetracycline,

aureomycin, terramycin, subtilin, amisomycin, and their derivatives.

It is preferable to react a sodium, potassium or any monovalent alkali metal form of the negatively-charged group with a salt form of the cationic antibiotic. Thus, OSO_3Na , OSO_3K , SO_3Na , SO_3K , OPO_3Na and OPO_3K are preferred as negatively-charged groups, although others as for example $(\text{OSO}_3)_2\text{Mg}$, $(\text{OSO}_3)_2\text{Ca}$, $(\text{SO}_3)_2\text{Zn}$ and $(\text{OPO}_3)_2\text{Ca}$ may be used. Commercially available heparin or TDMAC heparin may contain OSO_3 groups in various forms, e.g., OSO_3H , OSO_3Na , OSO_3K , $(\text{OSO}_3)_2\text{Ca}$, etc., and, as illustrated in Examples Nos. 2, and 4, steps may be taken to ensure conversion of all OSO_3 groups into OSO_3Na or OSO_3K . Preferably the cationic antibiotic in salt form has at least one amine group or a net pK_a of greater than 7.0. Suitable salt forms of cationic antibiotics include cationic antibiotic $\cdot \text{H}_2\text{OSO}_3$, HNO_3 , HCl , etc., as for example, tetracycline-HCl and polymyxin B-sulfate.

If the negatively charged group is in acid form, as for example OSO_3H , SO_3H and OPO_3H , it is preferable to react the negatively charged group with a base form of the cationic antibiotic.

The foregoing may be more particularly illustrated by the following examples:

EXAMPLE 1

One 10 mm by medical grade latex tubing obtained from Bard Urological Division of Murray Hill, New Jersey, was soaked in 50 ml of a 2% TDMAC-heparin complex solution for five seconds and air dried for one hour. The tubing was then rinsed in 1,000 ml of distilled water for 10 minutes and then soaked in 20 ml of a 0.2% gentamicin-sulfate solution for five minutes. Subsequently, it was rinsed in 1,000 ml $\text{d.H}_2\text{O}$ for 20 minutes and then air dried at room temperature overnight.

The tubing was dipped into *E.coli* suspension in saline at 1×10^6 colony forming units per cc, (CFU/cc) for five seconds and air-dried at room temperature for 30 minutes. Then it was placed on a nutrient agar plate and incubated at 37° for 48 hours. There was no bacterial growth on and around the experimental tubing. There was heavy growth around a control.

EXAMPLE 2

One 10 mm x 10mm polyethylene film obtained from Bard Urological Division was soaked in 50 ml TDMAC-Heparin solution for two hours and

then air-dried at room temperature for one minute. The film was immersed in 1,000 ml of 0.1% sodium carbonate for five minutes and rinsed in two volumes of 1,000 ml $\text{d.H}_2\text{O}$ for five minutes each with stirring. It was then immersed in 0.2% polymyxin-B sulfate solution in $\text{d.H}_2\text{O}$ for three minutes with stirring, rinsed in 1,000 ml $\text{d.H}_2\text{O}$ for one minute and air-dried at room temperature for one hour.

The film was dipped into *Staphylococcus aureus* suspension in saline at 1×10^6 CFU/cc for five seconds and air-dried at room temperature for 30 minutes. Then it was placed on a nutrient agar plate and incubated at 37°C for 48 hours. No growth was detected on or around the experimental film.

EXAMPLE 3

Dipped a 20mm x 30mm medical grade PVC film in 20 ml TDMAC-Heparin solution for one minute and air-dried at room temperature for five minutes. It was then rinsed in 1,000 ml $\text{d.H}_2\text{O}$ for 10 minutes, dipped into 20 ml of 0.2% tetracycline-HCl solution for three minutes and rinsed in 1,000 ml $\text{d.H}_2\text{O}$ for 10 minutes.

The dry film was dipped in 2cc of *E.coli* suspension in saline at 1×10^6 CFU/cc and then air-dried at room temperature for 30 minutes. It was then placed on a nutrient agar plate and incubated at 37°C for 48 hours. No bacterial growth was visible both microscopically and macroscopically on or around the experimental film.

EXAMPLE 4

One 1.5mm x 10mm x 10mm Dacron felt was soaked in 50 ml 2% TDMAC-Heparin for two hours and air-dried at room temperature for one hour. The felt was immersed in 1,000 ml 0.1% sodium bicarbonate solution for five minutes, two volumes of 1,000 ml $\text{d.H}_2\text{O}$ for five minutes each, 20 ml 0.2% polymyxin-B sulfate for three minutes, and then in 1,000 ml $\text{d.H}_2\text{O}$ for five minutes.

The felt was air-dried at room temperature overnight and dipped into 2cc of *Staphylococcus aureus* at 1×10^6 CFU/cc for three seconds. It was then air-dried, placed on a nutrient agar plate and incubated at 37°C for 48 hours. No bacterial growth was visible on or around the experimental felt.

EXAMPLE 5

A three mm piece of silicone catheter obtained from Bard Urological Division of Murray Hill, New Jersey is soaked in 50 ml of 5% BZK-heparin in isopropanol for 5 seconds and then air dried at room temperature for 30 minutes. It is then soaked in 10 mm of 0.1% tetracycline-HCl solution for five minutes at room temperature. Subsequently it is rinsed in 500 ml of distilled water with stirring for 30 seconds and then air dried.

The silicon catheter is subsequently placed in a petri dish containing E. coli and incubated for 48 hours. The catheter inhibits the growth of E.coli.

It should be understood that the foregoing description of the invention is intended merely as illustrative thereof and other modifications and embodiments may be apparent to those skilled in the art without departing from its spirit.

Claims

1. A medical device having long lasting bactericidal properties comprising,
a substrate,

said substrate carrying a negatively-charged group having a pKa of less than 6, and
a cationic antibiotic ionically bonded to said negatively-charged group.

2. A medical device as claimed in claim 1 wherein negatively-charged group is selected from the group consisting of sulphate, sulfonate and phosphate.

3. A medical device as claimed in claim 2 further comprising a carrier molecule partially composed of said negatively-charged group and bound to said substrate such that the negatively-charged group is exposed for ionic interaction with said cationic antibiotic.

4. A medical device as claimed in claim 3 further comprising an anchor molecule, said anchor molecule interposed between said carrier molecule and said substrate for binding said carrier molecule to said substrate.

5. A medical device as claimed in claim 4 wherein said substrate is substantially hydrophobic, said anchor molecule having a hydrophobic portion and a cationic portion, and said carrier molecule being heparin, said hydrophobic portion securing said anchor molecule to said substrate, and said cationic portion securing said heparin to said anchor.

6. A medical device as claimed in claim 5 wherein said anchor molecule is a surfactant.

7. A medical device as claimed in claim 6 wherein said surfactant is selected from the group consisting of BZK and TDMAC.

8. A medical device as claimed in claim 7 wherein said cationic antibiotic is selected from the group consisting of bacitracin, polymyxins, tyrothricin, viomycin, and vancomycin, neomycin, erythromycin, streptomycin, tobramycin, gentamicin, kanamycin, paromomycin, cycloserine, tetracycline, aureomycin, terramycin, subtilin, amisomycin, and their derivatives.

9. A medical device as claimed in claim 3 wherein said substrate is substantially hydrophobic and said carrier molecule is selected from the group consisting of ROSO_3^- , RSO_3^- and ROPO_3^- wherein R is a hydrophobic chain consisting essentially of carbon and hydrogen atoms and at least four carbon atoms long.

10. A medical device as claimed in claim 9 wherein said carrier molecule is a phospholipid.

11. A medical device as claimed in claim 10 wherein said cationic antibiotic is selected from the group consisting of bacitracin, polymyxins, tyrothricin, viomycin, and vancomycin, neomycin, erythromycin, streptomycin, tobramycin, gentamicin, kanamycin, paromomycin, cycloserine, tetracycline, aureomycin, terramycin, subtilin, amisomycin, and their derivatives.

12. A medical device as claimed in claim 3 wherein said substrate is provided with a positive charge, and said carrier molecule is bound to said substrate in a manner such that the negatively-charged group is exposed for ionic interaction with said cationic antibiotic.

13. A medical device as claimed in claim 12 wherein said carrier molecule is heparin.

14. A medical device as claimed in claim 13 wherein said cationic antibiotic is selected from the group consisting of bacitracin, polymyxins, tyrothricin, viomycin, and vancomycin, neomycin, erythromycin, streptomycin, tobramycin, gentamicin, kanamycin, paromomycin, cycloserine, tetracycline, aureomycin, terramycin, subtilin, amisomycin, and their derivatives.

15. A medical device as claimed in claim 2 wherein said negatively-charged group is provided on the surface of the substrate during the manufacture of the substrate.

16. In a medical device prepared from a substrate, a method of imparting said medical device with long lasting bactericidal properties comprising, providing said substrate with a negatively-charged group having a pKa value of less than 6, soaking said substrate in a cationic antibiotic containing solution, and drying said substrate.

17. A method as claimed in claim 16 wherein said negatively-charged group is selected from the group consisting of sulfate, sulfonate, and phosphate.

18. A method as claimed in claim 17 wherein

said negatively charged group is selected from the group consisting of OSO_3K , OSO_3Na , SO_3K , SO_3Na , OPO_3K and OPO_3Na and said cationic antibiotic is in salt form.

19. A method as claimed in claim 18 wherein said negatively-charged group is in acid form and said cationic antibiotic is in base form.

20. A method as claimed in claim 17 wherein said negatively-charged group is a portion of a carrier molecule and said carrier molecule is bound to said substrate such that the negatively-charged group is exposed for ionic interaction with said cationic antibiotic.

21. A method as claimed in claim 20 wherein said substrate is substantially hydrophobic and said carrier molecule is selected from the group consisting of ROSO_3 , RSO_3 and ROPO_3 , wherein R is a hydrophobic chain consisting essentially of carbon and hydrogen atoms and at least four carbon atoms long,

and said substrate is provided with said negatively-charged group by soaking said substrate in a solution containing said carrier molecule.

22. A method as claimed in claim 21 wherein said carrier molecule is a phospholipid.

23. A method as claimed in claim 20 wherein said carrier molecule is bound to said substrate via an anchor molecule.

24. A method as claimed in claim 23, wherein said carrier molecule is bound to said substrate by first ionically bonding said carrier molecule to said anchor molecule to form an anchor-carrier complex, and next

bonding the anchor portion of said anchor-carrier complex to said substrate.

25. A method as claimed in claim 24 wherein said carrier molecule is heparin and said anchor molecule is TDMAC, said anchor-carrier complex is formed by preparing a solution containing TDMAC and heparin in approximate molar equivalents, and said anchor portion of said anchor-carrier complex is bound to said substrate by soaking said substrate in said complex containing solution.

26. A method as claimed in claim 25, wherein said negatively charged group is selected from the group consisting of OSO_3K and OSO_3Na and said cationic antibiotic is selected from the group consisting of cationic antibiotics carrying at least one amine group and cationic antibiotics having a pKa greater than 7.

27. A method as claimed in claim 24 wherein said carrier molecule is heparin and said anchor molecule is BZK,

said anchor-carrier complex is formed by preparing a solution containing BZK and heparin, and

said anchor portion of said anchor-carrier complex is bound to said substrate by soaking said sub-

strate in said complex containing solution.

28. A method as claimed in claim 27 wherein said negatively charged group is selected from the group consisting of OSO_3K and OSO_3Na and said cationic antibiotic is selected from the group consisting of cationic antibiotics carrying at least one amine group and cationic antibiotics having a pKa greater than 7.

29. A method as claimed in claim 20 wherein said substrate is first provided with a positive charge, and

said carrier molecule is heparin and is bound to said substrate by soaking said substrate in a heparin containing solution.

30. A method as claimed in claim 17 wherein said negatively-charged group is provided on the surface of said substrate by manufacturing said negatively-charged group into the surface of the substrate.

31. A method as claimed in claim 30 wherein said medical device is prepared using a polymer selected from the group containing surface OSO_3^- , SO_3^- and surface OPO_3^- groups.

Amended claims in accordance with Rule 86(2) EPC.

1. A medical device having long-lasting bactericidal properties characterised by comprising a substrate, heparin molecules ionically bound to said substrate via anchor molecules, said anchor molecules attached directly to said substrate and interposed between said heparin molecules and said substrate, said anchor molecules selected from the group consisting of BZK and TDMAC, and cationic antibiotic molecules ionically bound to said heparin molecules.

2. A medical device as claimed in claim 1 characterised in that more than one cationic antibiotic molecule is bound to each molecule of heparin.

3. A medical device as claimed in either claim 1 or claim 2 characterised in that said cationic antibiotic is an aminoglycoside or a polypeptide antibiotic.

4. A medical device as claimed in any of claims 1-3 characterised in that said cationic antibiotic is selected from the group consisting of Polymyxin B and Gentamicin.

5. In a medical device prepared from a substrate, a method of imparting said medical device with long-lasting bactericidal properties, characterised by attaching anchor molecules selected from the group consisting of BZK and TDMAC directly to said substrate by soaking said substrate in a solution containing said anchor molecules, next soaking said substrate in a solution containing heparin molecules in monovalent metal salt form to

ionically bind said heparin molecules to said anchor molecules on said substrate, and then soaking said substrate in a solution containing a salt form of cationic antibiotic molecules to bind said cationic antibiotic molecules to said heparin.

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6. A method as claimed in claim 5 further characterised by binding more than one cationic antibiotic molecule to each molecule of heparin.

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EUROPEAN SEARCH REPORT

Application Number

EP 88 31 1520

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL3)
Y	US-A-4 749 585 (R.S. GRECO et al.) * Column 1, lines 45-50; column 2; column 3, lines 18-52; column 5, lines 22-68 *	1-31	A 61 L 27/00 A 61 L 33/00 A 61 L 29/00
Y	--- AU-B- 487 923 (SUTURES INC.) * Page 3, lines 1-4; page 4, lines 15-20; page 6, lines 16-30; page 7, lines 1-12; example 1 *	1-31	
A	--- US-A-3 987 797 (M. STEPHENSON) * Column 1, lines 62-65; column 6, lines 9-15; claims *	1-3	
Y	--- US-A-4 713 402 (D.D. SOLOMON) * Column 3, lines 10-25; column 4, lines 1-4; column 5, lines 7-14; examples 1,4 *	1-31	
D,A	--- US-A-4 442 133 (R.S. GRECO et al.)		
D,A	--- US-A-4 349 467 (J.L. WILLIAMS et al.)		
A	--- WO-A-8 600 795 (UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY) -----		
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 05-06-1989	Examiner ESPINOSA Y CARRETERO M.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	